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DOI:

[10.1038/ni.3856](https://doi.org/10.1038/ni.3856)

[10.1038/ni.3856](https://doi.org/10.1038/ni.3856)

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*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Linterman, MA & Toellner, K-M 2017, 'TFR cells trump autoimmune antibody responses to limit sedition', *Nature Immunology*, vol. 18, no. 11, pp. 1185-1186. <https://doi.org/10.1038/ni.3856>, <https://doi.org/10.1038/ni.3856>

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Final publication: *Nature Immunology* 18, 1185–1186 (2017) doi:10.1038/ni.3856 Published online 18 October 2017

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## **Tfr cells trump autoimmune antibody responses to limit sedition**

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**Interleukin 2 inhibits follicular T helper cells and promotes Foxp3-expressing regulatory T cell generation. Ballesteros-Tato and colleagues shows that things are more complex for Tfr cell generation.**

Germinal centers (GCs) form in secondary lymphoid tissues after infection or immunization, producing both memory B cells and antibody-secreting plasma cells that provide protection against subsequent infection<sup>1</sup>. GCs are absolutely dependent on T follicular helper (T<sub>FH</sub>) cells for their formation and maintenance, and contain a population of Foxp3<sup>+</sup> follicular regulatory T (T<sub>FR</sub>) cells whose biology has remained enigmatic since their discovery in 2011 (ref. 2). In this issue of *Nature Immunology*, Ballesteros-Tato and colleagues demonstrate an inhibitory role of interleukin 2 (IL-2) in T<sub>FR</sub> cell differentiation, and show that preventing T<sub>FR</sub> cell differentiation results in increased production of antibody-secreting plasma cells, including those with self-reactive specificity<sup>3</sup>.

In contrast to T<sub>FH</sub> cells, which provide help to GC B cells, T<sub>FR</sub> cells have a suppressive function and are thought to limit the GC response. Despite their regulatory capacity, T<sub>FR</sub> cells phenotypically resemble T<sub>FH</sub> cells, expressing CXCR5, PD-1, and Bcl-6, the transcription factor that is essential for both T<sub>FH</sub> and T<sub>FR</sub> cell differentiation<sup>4-6</sup>. One common feature of both T<sub>FH</sub> and T<sub>FR</sub> cells is that they do not express CD25, the  $\alpha$  chain of the high-affinity interleukin 2 (IL-2) receptor<sup>4,7,8</sup>. In primed CD4<sup>+</sup> T cells signaling via CD25 inhibits *Bcl6* expression, thereby preventing T<sub>FH</sub> cell differentiation<sup>2</sup>. However, it is not clear why T<sub>FR</sub> cells do not express CD25; this is especially paradoxical as Foxp3<sup>+</sup> regulatory T (T<sub>reg</sub>) cells require IL-2 signaling for their maintenance. Ballesteros-Tato and colleagues now show that abundance of IL-2 also suppresses T<sub>FR</sub> cell differentiation (**Fig. 1**)<sup>3</sup>. In the context of influenza

infection this mechanism delays the differentiation of T<sub>FR</sub> cells from Foxp3<sup>+</sup> precursors until IL-2 concentrations have declined. An inhibitory role of IL-2 on T<sub>FR</sub> cell formation was recently also reported by another group<sup>8</sup>. IL-2 suppresses T<sub>FH</sub> cell development by inducing STAT5 phosphorylation, a mechanism that is dependent on Blimp-1 expression<sup>2</sup>. Blimp-1 limits the size of the T<sub>FR</sub> cell population in a cell-intrinsic way<sup>4</sup>, and, interestingly, enhancing IL-2 availability in Blimp-1-deficient cells does not inhibit T<sub>FR</sub> cell accumulation, suggesting that an IL-2–STAT5–Blimp-1 axis represses T<sub>FR</sub> cell differentiation. However, not all Blimp-1-negative T<sub>reg</sub> cells are T<sub>FR</sub> cells, indicating that other signals events need to be delivered in parallel with IL-2 withdrawal before a T<sub>reg</sub> cell is able to become a T<sub>FR</sub> cell<sup>3</sup>.

Intriguingly, influenza infection yields IL-2 concentrations sufficient to inhibit T<sub>FR</sub>, but not T<sub>FH</sub>, cell differentiation<sup>3</sup>. This difference in responses to IL-2 may be because T<sub>FR</sub> cell precursors are more sensitive to IL-2 than T<sub>FH</sub> precursors, due to higher CD25 expression. CD25 is expressed by the majority of T<sub>reg</sub> cells and signaling via this receptor is essential for their survival and expansion under homeostatic conditions<sup>9</sup>. However, like T<sub>FR</sub> cells, some T<sub>reg</sub> cells do not express CD25; T<sub>reg</sub> cells expressing T-bet, the transcriptional regulator of T<sub>H</sub>1 cells, and T<sub>reg</sub> cells with an effector/memory phenotype have also down-regulated CD25 expression<sup>10,11</sup>. Taken together, these studies may intimate a model in which “naïve” T<sub>reg</sub> cells require IL-2 signaling for their maintenance, but that limiting IL-2 signaling is essential for T<sub>reg</sub> cells to differentiate into effector subsets or memory T<sub>reg</sub> cells.

The role that T<sub>FR</sub> cells play in GC biology has been difficult to decipher, with multiple studies yielding conflicting results. Initially this was because there was no mouse model that specifically lacked T<sub>FR</sub> cells. Because of this, all *in vivo* experiments were performed using mixed bone marrow chimeras or adoptive cell transfers, systems which have limitations. The generation of *Bcl6*<sup>flox/flox</sup>*Foxp3*<sup>cre</sup> animals provides a mouse that specifically lacks T<sub>FR</sub> cells<sup>12</sup>. Ballesteros-Tato and colleagues<sup>3</sup> use this model to demonstrate T<sub>FR</sub> cells control the formation of antibody-secreting cells. This dysregulation in the absence of T<sub>FR</sub> cells is not simply due to a change in magnitude of the response, as the antibody specificity is also altered: lack of T<sub>FR</sub> cells does not alter anti-influenza antibody titer, but increases production of anti-nuclear autoimmune antibodies after influenza infection. Consistent with the role

of IL-2 in limiting T<sub>FR</sub> cell formation, treating mice with recombinant IL-2 also results in autoantibody production<sup>3</sup>.

The finding that T<sub>FR</sub> cells limit the production of self-reactive antibody-secreting plasma cells is a key discovery in understanding the biology of these cells. Within the GC, B cells undergo somatic hypermutation of the genes encoding their B cell receptors. This mutation process is random and can result in the emergence of self-reactive clones. It is, therefore, essential that the selection of mutated GC B cells is stringent, ~~in order~~ to ensure these cells do not exit the GC as long-lived plasma cells or memory B cells. Selection within the GC is a process thought to be driven through positive feedback to B cells from follicular dendritic cells and T<sub>FH</sub> cells, while self-reactive B cells perish through neglect<sup>1</sup>. The discovery that, in the absence of T<sub>FR</sub> cells, B cells with a self-reactive B cell receptor can emerge from the GC suggests that these cells may have an active role in negative B cell selection. Alternatively, T<sub>FR</sub> cells may act to limit the provision of positive signals from either T<sub>FH</sub> cells or follicular dendritic cells. The mechanism by which T<sub>FR</sub> cells control autoreactivity from the GC, and the main cell types on whom they act are pertinent questions in understanding not just the role for T<sub>FR</sub> cells, but the biology of the GC.

#### Legend to Figure 1

When IL-2 binds the high affinity IL-2 receptor, composed of CD122, the common  $\gamma$  chain ( $\gamma c$ ) and CD25, STAT5 is phosphorylated leading to repression of Bcl6, and increase in Blimp1 expression. The lack of Bcl6 and increase in Blimp1 inhibits Tfr cell differentiation in Foxp3<sup>+</sup> precursors.

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